REMARKS

Objections to the Specification

The Examiner has objected to the Abstract in that it was submitted as the first page of the published version of the present application (WO 2004/099256). In response, on the "Amendments to Specification" page above, Applicants have instructed that the present Abstract be deleted and presented on a separate page with instructions to insert the Abstract on the last page of the application immediately following the claims, i.e., as new page 10. The new Abstract is substantially similar to the Abstract presented on the first page of WO 2004/099256 referred to by the Examiner, and therefore no new matter is added by the Abstract. A new page 10 is included herewith (Tab A).

Non-Statutory Obviousness-Type Double Patenting

The Examiner has raised a non-statutory obviousness-type double patenting rejection against Claims 1 and 4 of the present application as unpatentable over Claims 1 and 2 of U.S. Pat. No. 7,091,337 ("the '337 patent").

According to the Examiner,

> "Instant claim 1 is drawn to a process for depolymerization of a glycosaminoglycan comprising exposing the glycosaminoglycan to UV radiation . . . Claim 1 of '337 is also drawn to a process for depolymerization of a glycosaminoglycan via exposure of the glycosaminoglycan to radiation, which reads on UV radiation." (See, Office Action, page 3.)

Applicants have canceled Claim 4 and therefore the rejection as it applies to that claim is rendered moot.

Applicants believe the Examiner's characterization of the scope of Claim 1 of the '337 application omits a critical element of that patent's claimed process that is not an element of the claimed process of the present invention. Claim 1 of the '337 patent is directed to a process for the depolymerization of glycosaminoglycanes, comprising irradiating the glycosaminoglycanes with high energy radiation in the presence of an organic compound, e.g., methanol, ethanol, isopropanol, etc. However, Claim 1 of the present application as amended is patentably distinct from Claim 1 of the '337 patent. Claim 1 has been amended to be specifically directed to a process for the depolymerization of heparin, wherein the process results in at least a 50%

reduction in the M_w of the depolymerized heparin as compared with the M_w of the heparin prior to the start of the depolymerization process via exposure of the heparin to UV radiation having a peak of from 245nm to 260nm. The claimed process does not include the addition of any organic compound as required in Claim 1 of the '337 patent. Therefore, Applicants assert that the process claimed in the present invention for the depolymerization of heparin is patentably distinct from the process for the depolymerization of glycosaminoglycanes in the presence of an organic compound as claimed in Claim 1 of the '337 patent.

Reconsideration and allowance of Claim 1 are respectfully requested.

35 U.S.C. §102(b)

The Examiner has objected to Claims 1-4, 6, and 7 as anticipated by Balazs et al., *Radiation Research*, 11: 149-164 (1959) ("Balazs et al."). According to the Examiner,

> "Balazs et al. teach the depolymerization of hyaluronic acid (glycosaminoglycan) via irradiation of the hyaluronic acid with UV radiation from a low-pressure mercury lamp . . . The hyaluronic acid used as starting material had a molecular weight of 80,000 and the molecular weight of the depolymerized hyaluronic acid obtained was 19,700 (M_w less than 50% of the M_w of the starting glycosaminoglycan before irradiation . . . *Balazs et al. also teach that similar results were obtained on irradiating heparin with UV light.*" (See, Office Action, page 4.) (emphasis added.)

Applicants have canceled Claims 4 and 7 and therefore this objection is rendered moot with respect to those claims.

Applicants submit that, in contrast to the Examiner's assertion, Balazs et al. do not teach that results obtained following irradiation of heparin with UV light were similar to the results obtained following irradiation of hyaluronic acid with UV light. In fact, Applicants assert that due to critical differences between the molecular structure of heparin and hyaluronic acid, the results of irradiating hyaluronic acid with UV light are in no way indicative of the results that would be expected by one skilled in the art following irradiation of heparin with UV light and, as a matter of fact, the results reported by Balazs et al. prove this point.

First, it is well known in the art that hyaluronic acid has a much lower sulfur content than heparin and a major effect of this difference is that hyaluronic acid is depolymerized at a much faster rate than heparin when exposed to UV radiation. (See, Balazs et al., page 149-150, sulfur

content of hyaluronic acid prior to irradiation is **<0.1%** vs. **13.3%** sulfur content of heparin prior to irradiation.) A direct effect of the lower sulfur content of hyaluronic acid when irradiated with UV light is seen in the results of Figure 2. As seen with hyaluronic acid, specific viscosity (open circles) decreases rapidly to near 0 after less than 20 minutes of irradiation. According to Balazs et al., this is an indication of rapid degradation of the polysaccharide,

> "The degradation of polysaccharides . . . in the course of ionizing irradiation has been described by several authors [citations omitted]. The main evidence for the reported degradation was the decrease in viscosity . . . the viscosity of hyaluronic acid preparations decreased after a relatively short period of irradiation . . . The sedimentation and diffusion measurements indicate that this drop is due mainly to a decrease in molecular weight." (See, Balazs et al., paragraph bridging pages 161 and 162.)

In fact, as noted by the Examiner with respect to Balazs et al.,

> Hyaluronic acid prepared from the vitreous body by enzymatic hydrolysis of the proteins has a relatively low molecular weight (80,000) . . . The molecular weight of the degraded hyaluronic acid was found to be 19,700 . . ." (See, Balazs et al., paragraph bridging pages 161 and 162.)

The Examiner will note that no such data relating to reduction in viscosity or molecular weight is presented (or discussed) by Balazs et al. with respect to heparin, either before or after irradiation with UV light. However, the results presented in Figure 2 of Balazs et al. indicate that the molecular weight of heparin is decreased only slightly after exposure to the same level of irradiation that completely destroys the hyaluronic acid. As seen in Figure 2, the "% anticoagulation activity" data of heparin shows only a slight decrease and leveling off after 80 minutes of irradiation (at which time the hyaluronic acid has been completely destroyed). It is well known in the art that the % anticoagulation activity of heparin is directly related to the level of depolymerization, i.e., as depolymerization (and concomitant reduction in molecular weight) progresses, the % anticoagulation activity of heparin also decreases. As seen in Figure 2, an approximate 25% reduction in anticoagulation activity following 120 minutes of UV irradiation indicates that the molecular weight of the (still 75% active) heparin has not been reduced anywhere near 50%. In fact, from the heparin anticoagulation data, Balazs et al. only conclude,

> "The loss of anticoagulant activity indicates that the biological properties of the sulfated polysaccharides may change during irradiation." (See, Balazs et al., page 162.)

Therefore, Applicants assert that the Balazs et al. reference does not anticipate Applicants' claimed process for the depolymerization of heparin, which process reduces the molecular weight of the heparin by at least 50% as compared with the molecular weight of the heparin before irradiation. Due to the significant difference in the sulfur content between hyaluronic acid and heparin, one skilled in the art would not expect the data presented in Balazs et al. with respect to results obtained following UV irradiation of hyaluronic acid and in particular the reduction in molecular weight, would in any way reflect or indicate the results expected following UV irradiation of heparin and, in fact, Balazs et al. indicates that 120 minutes of UV irradiation has drastically different effects on heparin and hyaluronic acid. (See, Balazs et al., Figure 2.)

Therefore, the invention disclosed in Claims 1-3 and 6 as amended herein cannot be anticipated by the Balazs et al. reference as this references does not teach a process for the depolymerization of heparin wherein the molecular weight of the depolymerized heparin is at least 50% less than the molecular weight of the heparin before depolymerization, the process comprising exposing the heparin to UV irradiation have a peak of from 245nm to 260nm.

Reconsideration and allowance of Claims 1-3 and 6 are respectfully requested.

35 U.S.C. §103(a)

The Examiner has rejected Claim 5 under 35 U.S.C. §103 as unpatentable over Balazs et al *supra* in view of Mascellani et al., WO 90/04607.

Applicants have canceled Claim 5 and therefore the rejection as applied to this claim is rendered moot.

CONCLUSION

Applicants believe that Claims 1-3 and 6 define a novel method for the depolymerization of glycosaminoglycanes not disclosed by the cited art. Entry of the amendment to Claim 1 and allowance of Claims 1-3 and 6 are respectfully requested.

Applicants reserve the right to carry the subject matter of canceled Claims 5 and 7 forward in a continuation application for examination on the merits.

Respectfully submitted,

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